IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Confirmation No.: 2895
DeGRADO *et al.*	Art Unit: 1617
Appl. No. 10/801,951	Examiner: Chong, Yong Soo
Filed: March 17, 2004	Atty. Docket: 1694.0630003/JMC/M-R/KHR
For: **Facially Amphiphilic Polymers and Oligomers and Uses Thereof**	

Declaration of Harry Bermudez, Ph.D. Under 37 C.F.R. § 1.132

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

Sir:

I, the undersigned, Dr. Harry Bermudez, residing at 97 Howard St , Belchertown, MA 01003, USA, declare and state as follows:

1. A current *curriculum vitae* is appended hereto as Exhibit B1.

2. I received my Ph.D. degree in Chemical Engineering from the University of Pennsylvania in 2003. I am currently an Assistant Professor in the Department of Polymer Science & Engineering and an Adjunct Assistant Professor in the Department of Chemical Engineering at the University of Massachusetts Amherst. As seen from my attached *curriculum vitae*, I have published several papers and have received multiple awards related to biopolymers. Based on my education and experience, I have expertise in the field of biopolymers.

3. I have reviewed the above-captioned patent application ("patent application"), including the description and pending claims, and the final Office Action

dated October 30, 2007. I have also reviewed U.S. Patent No. 7,173,102 B2 to DeGrado *et al.* ("the '102 patent").

4. The invention claimed in the patent application relates to a method of treating an animal with a microbial infection by administering a pharmaceutical composition containing an amphiphilic oligomer of Formula II with 1 to about 20 monomer units and a pharmaceutically acceptable carrier or diluent.

5. It is my understanding the Examiner has rejected the claims of the patent application as being obvious over the '102 patent on the basis that it would have been obvious to a person of ordinary skill in the art to treat a microbial infection in an animal by administering a pharmaceutical composition comprising the preferred oligomers disclosed in the '102 patent.

6. For at least the reasons described below, I respectfully disagree with the Examiner's conclusion that a person of ordinary skill in the art would have been motivated to treat an animal with a microbial infection by administering a pharmaceutical composition containing an amphiphilic oligomer of Formula II with 1 to about 20 monomer units and a pharmaceutically acceptable carrier or diluent, as claimed in the patent application.

7. First, the '102 patent indicates that the disclosed polymers can be applied to, or dispersed throughout, an object and does not describe a method of treating a microbial infection in an animal. (The '102 patent, col. 4, lines 60-63; col. 30, lines 18-39.) It is my opinion these disclosures of the '102 patent direct a person of ordinary skill in the art to

apply the disclosed polymers to a surface, or to incorporate them into, an object, such as a contact lens or a catheter. Also, the disclosures in the '102 patent provide a person of ordinary skill in the art with no guidance as to how to formulate the polymers with a carrier or diluent. Additionally, the '102 patent does not disclose by what route the polymers may be administered, such as parenteral, oral, or transdermal administration. It is my opinion that a person of ordinary skill in the art would not expect that a polymer to be applied to the surface of, or incorporated into, an object would necessarily be effective when administered to an animal to treat a microbial infection. There is no disclosure in the '102 patent suggesting that the disclosed polymers could be used other than for surface applications. Thus, it is my opinion that a person of ordinary skill in the art would not have been motivated to treat an animal with a microbial infection by administering a pharmaceutical composition containing an amphiphilic oligomer of Formula II and a pharmaceutically acceptable carrier or diluent, as claimed in the patent application, in view of the '102 patent.

8. Second, the '102 patent discloses the polymers applied to the surface of an object are more prone to leach from the object if the polymers have a molecular weight of about 0.8 kD to about 20 kD. (*Id.*, at col. 5, lines 55-59.) Therefore, a person of ordinary skill in the art applying the polymers to the surface of an object would use a polymer with a molecular weight much greater than 20 kD to prevent or slow leaching of the polymer from the surface of the object. The '102 patent discloses the polymers have 2 to at least about 500 monomer units. (*Id.*, at col. 12, line 25.) As such, a person of ordinary skill in the art, when applying the polymers disclosed in the '102 patent to the surface of an object, would be motivated to use a polymer having a number of monomer units at the higher end of the disclosed range. The '102 patent clearly directs the skilled artisan to prevent the polymer

from leaching or escaping from the surface to which it is attached or incorporated. The currently pending claims recite an oligomer with a number of monomer units on the lower end of the range (m is 1 to about 20). Therefore, it is my opinion that a person of ordinary skill in the art would not expect that an oligomer containing only 1 to about 20 monomer units to be applied to the surface of an object would necessarily be effective when administered to an animal to treat a microbial infection. Thus, for at least this reason, it is my opinion that a person of ordinary skill in the art would not have been motivated to treat an animal with a microbial infection by administering a pharmaceutical composition containing an amphiphilic oligomer of Formula II with 1 to about 20 monomer units and a pharmaceutically acceptable carrier or diluent, as claimed in the patent application, in view of the '102 patent.

9. Third, a person of ordinary skill in the art would not read the disclosure in the '102 patent regarding the reduced toxicity of the polymers to birds, fish and mammals as indicative the polymers would be safe and effective if administered in a pharmaceutical composition to treat an animal with a microbial infection. A person of ordinary skill in the art knows the concentration of a polymer to be applied to a surface to prevent or slow growth of a microorganism is generally much lower than the concentration of the polymer included in a pharmaceutical composition to be administered to treat a microbial infection. Therefore, a person of ordinary skill in the art would be aware that the concentration of the polymer to be applied to a surface may not be toxic and would not assume the polymer would be safe if administered to an animal at the concentrations necessary to treat the microbial infection. Additionally, Example 6 only describes one *in vitro* experiment conducted to determine the toxic effect the polymers would have on human red blood cells.

A person of ordinary skill in the art would not assume from that a single *in vitro* experiment that the polymers described in the '102 patent are safe and effective and may be administered to an animal. Furthermore, a person of ordinary skill in the art would be concerned that a metabolite formed from the degradation of the polymer after administration may be toxic. The '102 patent provides no information regarding the toxicity of any metabolites. As such, a person of ordinary skill in the art would not conclude from this disclosure in the '102 patent the polymers would not be toxic and would be safe to be administered as a pharmaceutical composition to treat a mammal with a microbial infection. Thus, for at least this reason, it is my opinion that a person of ordinary skill in the art would not have been motivated to treat an animal with a microbial infection by administering a pharmaceutical composition containing an amphiphilic oligomer of Formula II and a pharmaceutically acceptable carrier or diluent, as claimed in the patent application, in view of the '102 patent.

10. For at least the reasons described above, it is my opinion that a person of ordinary skill in the art would not have been motivated to treat an animal with a microbial infection by administering a pharmaceutical composition containing an amphiphilic oligomer of Formula II with 1 to about 20 monomer units and a pharmaceutically acceptable carrier or diluent, as claimed in the patent application, in view of the '102 patent.

11. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of

Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the present patent application or any patent issued thereon.

Respectfully submitted,

Harry Hernandez, Ph.D.

Date: 6/20/2008
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Professional Preparation

1998	B.S., Chemical Engineering, University of Massachusetts Amherst
2003	Ph.D., Chemical Engineering, University of Pennsylvania
2003-04	Postdoctoral Fellow, Department of Materials, ETH Zurich, Switzerland
2004-06	Postdoctoral Fellow, Institute of Bioengineering, École Polytechnique Fédérale de Lausanne, Switzerland

Appointments

2007-	Assistant Professor, Dept. of Polymer Science & Engineering, University of Massachusetts Amherst
2007-	Adjunct Assistant Professor, Dept. of Chemical Engineering, University of Massachusetts Amherst

Selected Awards and Honors

2007	Armstrong Fund for Science
2007	Healey Endowment Faculty Research Grant
2000	Univ. of Pennsylvania Chemical Engineering Symposium, Best Poster Prize
1998	NSF Graduate Fellowship Honorable Mention
1997	American Chemical Society Scholar
1996, 97	Exxon Research & Engineering Scholarship

Representative Publications (out of 12 total)

[1] Bermudez, H. and Hathorne, A. P. Incorporating stimulus-responsive character into filamentous virus assemblies. *Faraday Discuss* **in press** (2008).

[2] Rothenfluh, D. A., Bermudez, H., O'Neil, C. P., and Hubbell, J. A. Biofunctional polymer nanoparticles for intra-articular targeting and retention in cartilage. *Nat Mater* **7**, 248–254 (2008).

[3] Photos, P. J., Bermudez, H., Aranda-Espinoza, H., Shillcock, J., and Discher, D. Nuclear pores and membrane holes: generic models for confined chains and entropic barriers in pore stabilization. *Soft Matter* **3**, 364–371 (2007).

[4] Bermudez, H., Hammer, D. A., and Discher, D. E. Effect of bilayer thickness on membrane bending rigidity. *Langmuir* **20**(3), 540–543 (2004).

[5] Bermudez, H., Brannan, A. K., Hammer, D. A., Bates, F. S., and Discher, D. E. Molecular weight dependence of polymersome membrane structure, elasticity, and stability. *Macromolecules* **35**(21), 8203–8208 (2002).

[6] Lee, J. C. M., Bermudez, H., Discher, B. M., Sheehan, M. A., Won, Y. Y., Bates, F. S., and Discher, D. E. Preparation, stability, and in vitro performance of vesicles made with diblock copolymers. *Biotechnol Bioeng* **73**(2), 135–145 (2001).

Synergistic Activities

- Mentor for undergraduate researchers: NSF-REU, Northeast Alliance SPUR
- AIChE: Session co-chair for Biomimetic Materials (2007)
- Ad-hoc reviewer for:
  - *Soft Matter* (Royal Society of Chemistry), *Colloid and Polymer Science* (Springer)

Collaborators & Other Affiliations

Collaborators & Co-Editors.

- Prof. Juan Anguita, Dept. of Veterinary & Animal Science, University of Massachusetts Amherst
- Prof. Helim Aranda Espinoza, Dept. of Bioengineering, University of Maryland, College Park
- Prof. Thomas Barker, Dept. of Biomedical Engineering, Georgia Institute of Technology
- Prof. James Watkins, Dept. of Polymer Science & Engineering, University of Massachusetts Amherst

Graduate Advisors and Postdoctoral Sponsors.

- Graduate co-advisors:
  - Dennis Discher, Department of Chemical Engineering, University of Pennsylvania
  - Daniel Hammer, Department of Bioengineering, University of Pennsylvania
- Postdoctoral: Jeffrey Hubbell, Institute of Bioengineering, École Polytechnique Fédérale de Lausanne

Thesis Advisor and Postgraduate-Scholar Sponsor.

- Graduate students (2):
  - Adam Hathorne, Ph.D. candidate in Polymer Science & Engineering (9/06-present)
  - Jung Won Keum, Ph.D. candidate in Chemical Engineering (12/07-present)
- Postdoctoral Associates (1): Ronald Lerum, Ph.D. Chemistry, Syracuse Univ. (2/08-present)
- Thesis committee:
  - Jessica Zimberlin, Ph.D. candidate in Polymer Science & Engineering. Advisor: A. Crosby

Invited lectures

2008 "Polymer and biopolymer presentation on nanostructured scaffolds". Department of Chemistry and Biozentrum, University of Basel, Switzerland.

2008 "Incorporating stimulus-responsive character into filamentous virus assemblies". Faraday Discussion 139: The Importance of Polymer Science for Biological Systems. Royal Society of Chemistry, York, U.K.

2008 "Coloides biologicos: controlando la presentacion de proteinas". 9th School on Molecular Biophysics. Universidad de Sonora, Hermosillo, Mexico

2007 "Altering the physical properties and functions of M13 bacteriophage". Department of Chemical Engineering, University of Massachusetts Amherst.

2006 "Probing the limits of self-assemblies and extending their functionality". Department of Chemistry, University of Sheffield, U.K.

2004 "The role of energy and length scales in the behavior of polymer vesicles". Europolymer conference (EUPOC). Gargnano, Italy.

Selected Conference presentations

2007 "Viruses and DNA as Nanoscale Building Blocks: Using Biology to Control Interactions", MRS Fall Meeting, Boston MA, USA.

2005 "The In Vivo Fate of Surface-Modified Bacteriophage", Society for Biomaterials Annual Conference. Memphis, TN.

2004 "Interfacial Reactivity in Block Copolymers: Understanding the Amphiphile-Hydrophile Transition". IUPAC World Polymer Congress. Paris, France.

Research Support

Pending.

- NSF: Broadening Participation Research Initiation Grants in Engineering
  "Engineering Stimulus-responsive Colloids with Elastin-like Polypeptides" (PI: 09/01/08 - 08/30/10).
  Total Direct Costs: $111,000
- NSF: Nanoscale Science and Engineering Center (SEED)
  "Design of heparin-based hybrid nanomaterials for tissue repair" (coPI with P. Dubin and I. Kaltashov)
  Total Direct Costs: $84,000

Current.

- Univ. of Massachusetts: Healey Endowment Faculty Research Grant
  "Dynamic Surfaces to Control Cell Motility" (PI: 05/01/07 - 05/31/09)
  Total Direct Costs: $28,000
- Univ. of Massachusetts: Armstrong Fund for Science
  "Modulating Cellular Recognition Using Peptide Motifs" (PI: 07/01/07 - 06/30/08)
  Total Direct Costs: $22,500
- NSF: Materials Research Science and Engineering Center
  "IRGIII - Aqueous Polymer Assembly" (Participant: 05/01/07 - 04/30/08)
  Total Direct Costs: $27,000
- NSF: Nanoscale Science and Engineering Center
  "TRG3 - Bionanotechnology" (Participant: 09/01/07 - 03/31/08)
  Total Direct Costs: $18,000